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 NEWS  8  MAR 03   REGISTRY/ZREGISTRY - Sequence annotations enhanced
 NEWS  9  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS  10 MAR 22   KOREAPAT now updated monthly; patent information enhanced
 NEWS  11 MAR 22   Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS  12 MAR 22   PATDPASPC - New patent database available
 NEWS  13 MAR 22   REGISTRY/ZREGISTRY enhanced with experimental property tags
 NEWS  14 APR 04   EPFULL enhanced with additional patent information and new
                   fields
 NEWS  15 APR 04   EMBASE - Database reloaded and enhanced
 NEWS  16 APR 18   New CAS Information Use Policies available online
 NEWS  17 APR 25   Patent searching, including current-awareness alerts (SDIs),
                   based on application date in CA/CAplus and USPATFULL/USPAT2
                   may be affected by a change in filing date for U.S.
                   applications.
 NEWS  18 APR 28   Improved searching of U.S. Patent Classifications for
                   U.S. patent records in CA/CAplus

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

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=> file .pub
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'MEDLINE' ENTERED AT 21:09:10 ON 09 MAY 2005

FILE 'BIOSIS' ENTERED AT 21:09:10 ON 09 MAY 2005
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=> integrin and (inhibit? or activat? or alloster?)
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=> s integrin and (inhibit? or activat? or alloster?)
L1        24725 INTEGRIN AND (INHIBIT? OR ACTIVAT? OR ALLOSTER?)

=> s l1 and diaryl
L2            2 L1 AND DIARYL

=> d 1-2 bib ab

L2   ANSWER 1 OF 2     MEDLINE on STN
AN   2001025013     MEDLINE
DN   PubMed ID: 11052808
TI   Discovery of novel p-arylthio cinnamides as antagonists of leukocyte
     function-associated antigen-1/intracellular adhesion molecule-1
     interaction. 1. Identification of an additional binding pocket based on an
     anilino diaryl sulfide lead.
AU   Liu G; Link J T; Pei Z; Reilly E B; Leitza S; Nguyen B; Marsh K C;
     Okasinski G F; von Geldern T W; Ormes M; Fowler K; Gallatin M
CS   Metabolic Disease Research and Drug Analysis Department, Pharmaceutical
     Products Division, Abbott Laboratories, Abbott Park, Illinois 60064-6098,
     USA.. Gang.Liu@abbott.com
SO   Journal of medicinal chemistry, (2000 Oct 19) 43 (21) 4025-40.
     Journal code: 9716531. ISSN: 0022-2623.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200011
ED   Entered STN: 20010322
     Last Updated on STN: 20010322
     Entered Medline: 20001116
AB   The interaction between leukocyte function-associated antigen-1 (LFA-1), a
     member of the beta(2)-integrin family of adhesion molecules, and
     intracellular adhesion molecule ICAM-1 (cd54) is thought to play a
     critical role in the inflammatory process.  On the basis of an anilino
     diaryl sulfide screening lead 1, in combination with pharmacophore
     analysis of other screening hits, we have identified an adjacent binding
     pocket.  Subsequently, a p-ethenylcarbonyl linker was discovered to be
     optimal for accessing this binding site.  Solution-phase parallel
     synthesis enabled rapid optimization of the cinnamides for this pocket.
     In conjunction with fine-tuning of the diaryl substituents, we
     discovered a novel series of potent, nonpeptide inhibitors of
     LFA-1/ICAM-1 interaction, exemplified by A-286982 (28h), which has IC(50)
     values of 44 and 35 nM in an LFA-1/ICAM-1 binding assay and LFA-1-mediated
     cellular adhesion assay, respectively.

L2   ANSWER 2 OF 2  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation  on STN
AN   2000:542948  BIOSIS
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DN PREV200000542948

TI Discovery of novel p-arylthio cinnamides as antagonists of leukocyte function-associated antigen-1/intracellular adhesion molecule-1 interaction. 1. Identification of an additional binding pocket based on an anilino **diaryl** sulfide lead.

AU Liu, Gang [Reprint author]; Link, J. T.; Pei, Zhonghua; Reilly, Edward B.; Leitza, Sandra; Nguyen, Bach; Marsh, Kennan C.; Okasinski, Gregory F.; von Geldern, Thomas W.; Ormes, Mark; Fowler, Kerry; Gallatin, Mike

CS Abbott Laboratories, 100 Abbott Park Rd., D-47R, AP-10, Abbott Park, IL, 60064-6098: Gang.Liu@abbott.com, USA

SO Journal of Medicinal Chemistry, (October 19, 2000) Vol. 43, No. 21, pp. 4025-4040. print.
CODEN: JMCMAR. ISSN: 0022-2623.

DT Article

LA English

ED Entered STN: 13 Dec 2000
Last Updated on STN: 11 Jan 2002

AB The interaction between leukocyte function-associated antigen-1 (LFA-1), a member of the beta2-**integrin** family of adhesion molecules, and intracellular adhesion molecule ICAM-1 (cd54) is thought to play a critical role in the inflammatory process. On the basis of anilino **diaryl** sulfide screening lead 1, in combination with pharmacophore analysis of other screening hits, we have identified an adjacent binding pocket. Subsequently, a p-ethenylcarbonyl linker was discovered to be optimal for accessing this binding site. Solution-phase parallel synthesis enabled rapid optimization of the cinnamides for this pocket. In conjunction with fine-tuning of the **diaryl** substituents, we discovered a novel series of potent, nonpeptide **inhibitors** of LFA-1/ICAM-1 interaction, exemplified by A-286982 (28h), which has IC50 values of 44 and 35 nM in an LFA-1/ICAM-1 binding assay and LFA-1-mediated cellular adhesion assay, respectively.

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 NEWS  12  MAR 22  PATDPASPC - New patent database available
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 NEWS  14  APR 04  EPFULL enhanced with additional patent information and new
                   fields
 NEWS  15  APR 04  EMBASE - Database reloaded and enhanced
 NEWS  16  APR 18  New CAS Information Use Policies available online
 NEWS  17  APR 25  Patent searching, including current-awareness alerts (SDIs),
                   based on application date in CA/CAplus and USPATFULL/USPAT2
                   may be affected by a change in filing date for U.S.
                   applications.
 NEWS  18  APR 28  Improved searching of U.S. Patent Classifications for
                   U.S. patent records in CA/CAplus

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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FILE 'BIOSIS' ENTERED AT 20:17:42 ON 09 MAY 2005
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=> s (alloster? or inhibit? or activat?) and (integrin)
L1       24725 (ALLOSTER? OR INHIBIT? OR ACTIVAT?) AND (INTEGRIN)

=> s l1 and review/dt
L2        1532 L1 AND REVIEW/DT

=> s l2 and allosteric
L3           8 L2 AND ALLOSTERIC

=> duplicate remove l3
PROCESSING COMPLETED FOR L3
L4           8 DUPLICATE REMOVE L3 (0 DUPLICATES REMOVED)

=> d 1-8 bib ab

L4   ANSWER 1 OF 8     MEDLINE on STN
AN   2004572372     MEDLINE
DN   PubMed ID: 15544539
TI   Therapeutic antagonists and the conformational regulation of the beta2
     integrins.
AU   Shimaoka Motomu; Springer Timothy A
CS   The CBR Institute for Biomedical Research, Department of Anesthesia and
     Pathology, Harvard Medical School, 200 Longwood, Boston, MA 02115, USA.
SO   Current topics in medicinal chemistry, (2004) 4 (14) 1485-95.  Ref: 76
     Journal code: 101119673. ISSN: 1568-0266.
CY   Netherlands
DT   Journal; Article; (JOURNAL ARTICLE)
       General Review; (REVIEW)
     (REVIEW, TUTORIAL)
LA   English
FS   Priority Journals
EM   200503
ED   Entered STN: 20041117
     Last Updated on STN: 20050309
     Entered Medline: 20050308
AB   The beta2 integrins are validated therapeutic targets for
     inflammatory disorders.  Two distinct mechanistic classes of small
     molecule inhibitors, termed alpha I allosteric and
     alpha/beta I-like allosteric antagonist, have recently been
     developed.  The alpha I allosteric antagonists bind underneath
     the C-terminal helix of the I domain and stabilize the I domain in the
     inactive closed conformation.  By contrast, the alpha/beta I-like
     allosteric antagonists bind to the beta2 I-like domain MIDAS and
     disrupt conformational signal transmission between the I and the I-like
     domain, leaving the I domain in a default inactive form.  Furthermore, the
     two classes of the antagonists have opposite effects on integrin
     conformation; the alpha I allosteric antagonists stabilize the
     bent conformation, whereas the alpha/beta I-like allosteric
     antagonists induce the extended conformation with inactive I domain.  The
     small molecule antagonists to the beta2 integrin highlight the
     importance of the structural linkages within and between integrin
     domains for transmission of the conformational signals and regulation of
     the overall conformation.
```

L4 ANSWER 2 OF 8 MEDLINE on STN
AN 2003180148 MEDLINE
DN PubMed ID: 12699076
TI Lymphocyte function-associated antigen-1 blockade by statins: molecular basis and biological relevance.
AU Weitz-Schmidt Gabriele
CS Novartis Pharma AG, Preclinical Research, Basel, Switzerland.. gabriele.weitz@pharma.novartis.com
SO Endothelium : journal of endothelial cell research, (2003) 10 (1) 43-7. Ref: 41
Journal code: 9412590. ISSN: 1062-3329.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200308
ED Entered STN: 20030418
Last Updated on STN: 20030802
Entered Medline: 20030801
AB Lymphocyte function-associated antigen-1 (LFA-1) belongs to the **integrin** family and plays an important role in leukocyte trafficking and in T-cell **activation**. Random screening of chemical libraries identified the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase **inhibitor** lovastatin as an **inhibitor** of the LFA-1/intercellular adhesion molecule (ICAM)-1 interaction. The effect of lovastatin on LFA-1 was found to be unrelated to the **inhibition** of HMG-CoA reductase and to be mediated by lovastatin binding to a novel **allosteric** site within LFA-1. The biological relevance of LFA-1 **inhibition** by statins with respect to the overall benefit of this drug class is reviewed. The implications of the statin effect on LFA-1 for future drug design and therapy are discussed.

L4 ANSWER 3 OF 8 MEDLINE on STN
AN 2002486520 MEDLINE
DN PubMed ID: 12297042
TI **Integrins**: bidirectional, **allosteric** signaling machines.
AU Hynes Richard O
CS Howard Hughes Medical Institute, Center for Cancer Research, Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.. rohynes@mit.edu
SO Cell, (2002 Sep 20) 110 (6) 673-87. Ref: 119
Journal code: 0413066. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; Space Life Sciences
EM 200210
ED Entered STN: 20020926
Last Updated on STN: 20021217
Entered Medline: 20021023
AB In their roles as major adhesion receptors, **integrins** signal across the plasma membrane in both directions. Recent structural and cell biological data suggest models for how **integrins** transmit signals between their extracellular ligand binding adhesion sites and their cytoplasmic domains, which link to the cytoskeleton and to signal transduction pathways. Long-range conformational changes couple these functions via **allosteric** equilibria.

L4 ANSWER 4 OF 8 MEDLINE on STN
AN 2002409074 MEDLINE
DN PubMed ID: 12163068
TI Engineering and design of ligand-induced conformational change in proteins.
AU Mizoue Laura S; Chazin Walter J
CS Department of Biochemistry, Center for Structural Biology, 896 PRB, Vanderbilt University, Nashville, TN 37232-0146, USA.. l.mizoue@vanderbilt.edu
SO Current opinion in structural biology, (2002 Aug) 12 (4) 459-63. Ref: 46
Journal code: 9107784. ISSN: 0959-440X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 20020807
Last Updated on STN: 20030130
Entered Medline: 20030129
AB The ability to manipulate ligand-induced conformational change, although representing a major challenge to the protein engineer, is an essential end point in efforts to produce novel functional proteins for biotechnology and therapeutic applications. Progress towards this goal requires determining not only what factors control the fold and stability of a protein, but also how ligand binding alters the complex conformational/energetic landscape. Important strides are being made on several fronts, including understanding the origin of long-range effects and **allosteric** structural mechanisms, using both experimental and theoretical approaches.

L4 ANSWER 5 OF 8 MEDLINE on STN
AN 1999254236 MEDLINE
DN PubMed ID: 10320933
TI Towards a structural model of an **integrin**.
AU Humphries M J
CS Wellcome Trust Centre for Cell-Matrix Research, School of Biological Sciences, University of Manchester, U.K.
SO Biochemical Society symposium, (1999) 65 63-78. Ref: 34
Journal code: 7506896. ISSN: 0067-8694.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199906
ED Entered STN: 19990714
Last Updated on STN: 20000303
Entered Medline: 19990629
AB **Integrins** are currently viewed as the principal family of extracellular matrix receptors. The interactions mediated by **integrins** are responsible for certain typical properties of adhesive cells, such as attachment and migration, but these molecules are also recognized to contribute to intracellular signalling processes, either by transducing signals themselves or by enabling and/or coordinating signalling via other receptor systems. As yet, the structural basis of **integrin** function is unknown, although detailed computer-based predictions have suggested working models for **integrin** tertiary structure. In this chapter, I will review this information and discuss recent studies examining the molecular basis of **integrin** regulation using stimulatory and **inhibitory** monoclonal antibodies (mAbs). Through the use of sensitive isolated

integrin-binding assays, stimulatory mAbs have been found to function either by inducing shape changes in **integrins** or by selectively recognizing and stabilizing active and ligand-occupied conformations of **integrins**, while blocking mAbs were found to be **allosteric inhibitors** of ligand binding that report specific ligand engagement events. This information has improved our understanding of the composition of the **integrin** ligand-binding pocket and the structural basis of **integrin activation**
.

L4 ANSWER 6 OF 8 MEDLINE on STN
AN 97298120 MEDLINE
DN PubMed ID: 9153268
TI Cell adhesion in vascular biology. New insights into **integrin** -ligand interaction.
AU Loftus J C; Liddington R C
CS The Mayo Clinic Arizona, Scottsdale, Arizona 85259, USA.
NC HL-42977 (NHLBI)
SO Journal of clinical investigation, (1997 May 15) 99 (10) 2302-6. Ref: 34
Journal code: 7802877. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Space Life Sciences
EM 199706
ED Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970617

L4 ANSWER 7 OF 8 MEDLINE on STN
AN 97092314 MEDLINE
DN PubMed ID: 8937979
TI Getting **integrins** into shape: recent insights into how **integrin** activity is regulated by conformational changes.
AU Mould A P
CS Wellcome Trust Centre for Cell-Matrix Research, School of Biological Sciences, University of Manchester, UK.. pmould@fs2.scg.man.ac.uk
SO Journal of cell science, (1996 Nov) 109 (Pt 11) 2613-8. Ref: 56
Journal code: 0052457. ISSN: 0021-9533.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970609
Last Updated on STN: 19970609
Entered Medline: 19970523

L4 ANSWER 8 OF 8 MEDLINE on STN
AN 94051535 MEDLINE
DN PubMed ID: 1364116
TI Cellular immune and cytokine pathways resulting in tissue factor expression and relevance to septic shock.
AU Edgington T S; Mackman N; Fan S T; Ruf W
CS Department of Immunology, Scripps Research Institute, La Jolla, CA 92037.
SO Nouvelle revue francaise d'hematologie, (1992) 34 Suppl S15-27. Ref: 103
Journal code: 7909092.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LA English
FS Priority Journals
EM 199312
ED Entered STN: 19940117
Last Updated on STN: 19950206
Entered Medline: 19931209

AB Cells of monocyte lineage serve as effector cells in the cellular immune response. In addition, they respond to LPS and cytokines with **activation** and expression of inflammatory effector gene products similar to those elicited by the antigen driven response. The response to antigen proceeds at the T helper cell level through two independent forms of cellular collaboration, contact and lymphokine. We review the control of expression of the Tissue Factor (TF) gene and the function of the TF protein. The enhanced initiation of transcription of the TF gene appears to require engagement of a 56 bp LPS Response Element, an enhancer that is engaged by both AP-1 type heterodimeric complexes as well as NF kappa B like heterodimeric complexes. Dissociation of NF kappa B from Ig kappa B by cytokine and LPS stimulation, and possibly **activated** T cells, may represent a common pathway to induction of the TF and other inflammatory genes. Enhancement of expression of TF is observed upon adhesion of Mo to endothelial cells and extracellular matrix proteins, as well as upon engagement of leukocyte **integrins**. The biological effects that follow from expression of TF by vascular cells have been resolved by analysis of function aided by the use of recombinant full length TF and truncated surface domain of TF. The rules of assembly of the cognate ligands of TF, namely the zymogen plasma factors VII and the serine protease factor VIIa, with the soluble surface domain of TF in free solution, in the presence of phospholipid surfaces and cell surface and of the anchored TF molecule have been described. It is evident that assembly of the surface domain of TF with VIIa to form the binary TF.VIIa complex induces a significant increase in the Kcat of the catalytic domain of VIIa for small peptidyl substrates and more profoundly for protein substrate. This provides substantial evidence for an **allosteric** effect on the catalytic cleft of VIIa that is imparted by binding to TF, its cognate catalytic cofactor. It is also evident that the TF.VIIa complex is proteolytically active and can **activate** the zymogen plasma factor X to the serine protease Xa in free solution, inferring that extended substrate recognition by induced structural loci of the TF.VIIa complex are created from either or both proteins to constitute a new recognition structure. It is also evident that association of X with charged phospholipid surfaces enhances the proteolytic **activation** of this zymogen by increasing recognition and susceptibility of the sessile peptide bond deduced from the markedly decreased Km and increased Kcat.(ABSTRACT TRUNCATED AT 400 WORDS)